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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

(C)

Office Action Summary	Application No.	Applicant(s)	
	08/852,020	MARUYAMA ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of a response filed 9/15/2003 to the previous office action (mailed 3/13/2003 as Paper No. 38). No changes to the claims or specification were made in applicants' response. The arguments presented in the response have been fully considered, but are not deemed persuasive for reasons that are summarized below. This action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office action mailed 3/13/2003 as Paper No. 38, which grounds for rejection are repeated below.**

Claims 57-60 encompass recombinant lambdoid bacteriophage vectors or bacteriophage having a cistron comprising the coding sequence for an anchor matrix gene operatively linked to coding sequences for a linker polypeptide and a desired, preselected polypeptide such that expression of the recombinant cistron during morphogenesis results in incorporation and display of the recombinant fusion polypeptide comprising the desired polypeptide sequence on the surface of the mature lambdoid phage particle. The claims encompass any of the head or tail

polypeptides (e.g. head proteins: pE, pD, pW, pFII, pB*, pX1, pX2; tail proteins: pV, pJ, pG, pM and pT; page 22 lines 13-21), or portions thereof, as the matrix anchor component of the fusion polypeptide that is displayed on the surface of the phage particle. Each of these polypeptides has its own unique structure and plays a unique role in phage morphogenesis, having a distinct set of temporal and spatial interactions with other phage proteins during the assembly of the mature phage particle. Thus, the instant claims are very broad genus claims directed to a number of distinct structural polypeptides having different structural and functional characteristics.

While the specification has described adequately one subset of the claimed genus, those embodiments drawn to the tail polypeptide pV, there is only the broadest description of any of the remaining members of the genus. The claims and specification only describe a conditionally expressible cistron encoding an anchor matrix polypeptide operatively linked to a linker polypeptide coding sequence which is in turn linked to the coding sequence for a desired, preselected polypeptide. There is no description of where within the coding sequence for any of the other members of the genus of potential anchor matrix polypeptides one would insert the sequences for the linker polypeptide and the desired polypeptide. There is no description in the prior art or within the specification as to which portions of any of the other anchor matrix polypeptides might be dispensable for morphogenesis and thus potentially suitable for insertion of foreign sequences. There are no relevant examples in the specification as filed of such a fusion construct for any of the potential anchor matrix polypeptides other than for pV. Because of the unique sequences, structural features and functions for each of the other anchor matrix proteins, one of skill in the art can not extrapolate from the description of fusion constructs comprising pV what would be a permissible insertion and fusion for any of the other anchor

matrix proteins such that a recombinant polypeptide expressed from such a construct would be assembled and displayed on the surface of the mature phage particle.

The art teaches that the process of phage morphogenesis is exceedingly complex. Moody provides a post-filing review of phage assembly that describes how different types of phage have tackled the problem of encapsulating the phage genetic material in a protective structure that itself relies on a minimum of genetic information to encode the head structure (Michael F. Moody. Journal of Molecular Biology 1999, Vol. 293, pages 401-433; see the entire document). Generally speaking this involves using a minimum number of different protein subunits (i.e. requiring less genetic information) to form a complex 3-dimensional structure that can accommodate the genetic material (e.g. an icosahedron in the case of large dsDNA bacteriophage). To do this the major head protein subunits must be able to interact with one another in *equivalent* and *quasi-equivalent* ways that involve several protein-protein interactions for each subunit monomer. For example, the different head structures for different types of phage heads shown in Figure 3 each show how a single protein monomer (represented by the smaller triangles) can interact with itself to form axes of 5-fold or 6-fold symmetry within the same structure. Thus, at each vertex in the structures shown in Figure 3, each monomer of the major head protein can have a 5-fold or 6-fold interaction with adjacent proteins.

Moody teaches that as the required size of the phage head increases (i.e. to encapsulate a larger viral genome) additional proteins are required to help deal with an increased requirement for quasi-equivalent interactions amongst the subunits in assembly of the head structure. For example, these proteins would include endoscaffolding or exoscaffolding proteins and/or other proteins that can remain as part of the mature phage head (e.g. page 404, last paragraph of

column 1 to column 2, second paragraph; page 407, column 1 to page 408, column 2). Moody teaches that assembly of the phage head is a complex process that is liable to errors, resulting in malformed heads such as tubes, spirals or polyhedrons (e.g. page 408, column 2 to page 411, column 1). Moody further teaches that all of the larger dsDNA phage heads undergo some sort of maturation to form a more stable, stronger structure that is more resistant to mechanical or chemical stress and that results in a simultaneous increase in head volume (e.g. page 413, column 2 to page 416, column 1). This process involves modification of at least one of the phage head proteins such as proteolytic cleavage (e.g. T-even phage) or chemical modification (e.g. phage P22, lambda or T7). In the maturation process the protein-protein interactions of the subunits of the phage head are necessarily altered, even resulting in the translocation of subunit domains from the inner to the outer surface of the phage head (e.g. in phage T4) (page 414, columns 1-2). Thus, phage head assembly is a complex process, involving multiple protein-protein interactions that change during the process and involving several different types of proteins.

Given the great complexity of the claimed invention, wherein the fusion protein of the invention is displayed on the surface of the phage particle, as evidenced by the teachings of Moody, it would be helpful to be able to reliably predict the functional/structural characteristics of a given fusion protein based upon its primary sequence alone. Unfortunately, the art teaches that the relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its activity), is not well understood and is not predictable as evidenced by Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights

of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and failures to make it predictable. Thus, as taught by Berendsen, it is likely that the first envisioned modification of a lambda phage head or tail protein to include a heterologous sequence would not be successful because one cannot predict a priori the final structure and functional characteristics of the fusion protein based upon primary sequence alone.

Given the broad genus of possible fusion proteins encompassed by the rejected claims and the lack of teachings in the instant specification or prior art that provide a basis for the skilled artisan to envision specific embodiments of the claimed invention, it would not have been possible for the skilled artisan to envision a representative number of the remaining members of the broadly claimed genus of recombinant anchor-matrix fusion proteins. Therefore, there is not sufficient description in the specification to inform a skilled artisan that the applicant was in possession of the full, large genus of recombinant phage embraced by the claimed invention: a recombinant lambdoid bacteriophage vector or bacteriophage comprising a cistron encoding an head or tail polypeptide other than pV operatively linked to the coding sequence for a linker polypeptide and desired, preselected polypeptide for display of the recombinant fusion protein on the surface of the mature phage.

Response to Arguments/Written Description

Applicant's arguments filed in the response of 9/15/2003 have been fully considered but they are not persuasive. The response essentially argues: **1)** the examiner's assertions regarding coding sequence locations, anchor matrix polypeptide portions dispensable for morphogenesis and lack of relevant examples are irrelevant to the written description requirement as they are not

limitations of the claims, **2)** literal support is present in the specification for the recited limitations of the rejected claims, and **3)** the specification provides explicit lists of the appropriate head or tail proteins that can be used in the instant invention.

Issues regarding the construction of functional recombinant lambdoid bacteriophage vectors are entirely relevant to the issue of written description on at least two grounds. First, the term "recombinant lambdoid bacteriophage" can be interpreted broadly to encompass a bacteriophage as well as a nucleic acid vector. In other words, claims 57-58 read on a fully formed bacteriophage particle comprising the nucleic acid sequences recited in the claims. Claims 59-60 are explicitly drawn to a lambdoid bacteriophage comprising the recited fusion protein. In each case, the assembly of the mature bacteriophage particle is dependent on each of the factors cited by the examiner in making the rejection. Knowledge of these factors (e.g. coding sequence locations, anchor matrix polypeptide portions dispensable for morphogenesis, etc.) would allow the examiner to more reliably envision those additional embodiments of the claimed invention that would necessarily satisfy the limitation of forming a mature bacteriophage particle. Given the enormous genus of vectors and phage particles embraced by the rejected claims and the lack of any significant description of these elements, the skilled artisan would not be able to envision even a single specific embodiment of the claimed invention (i.e. with regard to the exact construction of such a vector with regard to, for example, insertion of heterologous sequences into the matrix protein). Secondly, the entire specification is directed to the use of nucleic acid molecules comprising the elements recited in the rejected claims to functionally display desired sequences on the surface of the recombinant lambdoid phage particle. No other utility is suggested in the instant specification for any embodiment that does *not* functionally

display a desired polypeptide sequence as part of a fusion protein on the surface of a lambdoid phage particle.

The examiner does not contest that there is literal support for the limitations recited in the rejected claims. This is not a New Matter rejection. The grounds of rejection are directed to a lack of sufficient description to describe the broadly claimed genus of bacteriophage vectors encompassed by the claims. The fact that the specification asserts that any number of lambda surface proteins can be used in their invention for displaying fusion polypeptides on the surface of lambda phage does not provide a basis for the skilled artisan to envision those specific embodiments that satisfy the limitations of the claims. The examiner has provided a reasoned analysis based upon the description provided by the instant application and the teachings of the prior art concerning bacteriophage morphology and assembly that makes clear that an assertion that such fusion proteins can be made and used to functionally display a desired polypeptide on the surface of the phage head does not allow the skilled artisan to reliably envision even one embodiment where such a bacteriophage particle is produced.

Claims 57-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant lambdoid bacteriophage vector or bacteriophage comprising fusions with lambdoid bacteriophage tail polypeptides that are pV, does not reasonably provide enablement for embodiments wherein the lambdoid phage anchor matrix protein is other than pV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record**

in the office action mailed 3/13/2003 as Paper No. 38, which grounds for rejection are repeated below.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The nature of the invention is complex, involving a recombinant lambdoid bacteriophage which displays on the surface of the bacteriophage a fusion protein including one of the anchor matrix proteins operatively linked in the direction of the amino terminus to the carboxy terminus to a linker polypeptide and a polypeptide of choice. This invention further involves complex issues of which phage matrix polypeptides are suitable for forming such fusion proteins both in terms of accessible display on the outer surface of the phage and in the ability of the phage to assemble properly once the fusion protein is expressed during morphogenesis. Once a suitable matrix polypeptide has been identified, there are still complex issues as to where to insert the linker and preselected polypeptide into the desired matrix polypeptide such that assembly is not impaired and accessible display is maintained. Issues of what size and type of polypeptide will be tolerated and displayed in an accessible manner for each desired polypeptide are also present for the instant claims.

Assembly of the phage head is a complex process. Moody provides a post-filing review of phage assembly that describes how different types of phage have tackled the problem of encapsulating the phage genetic material in a protective structure that itself relies on a minimum

of genetic information to encode the head structure (Michael F. Moody. Journal of Molecular Biology 1999, Vol. 293, pages 401-433; see the entire document). Generally speaking this involves using a minimum number of different protein subunits (i.e. requiring less genetic information) to form a complex 3-dimensional structure that can accommodate the genetic material (e.g. an icosahedron in the case of large dsDNA bacteriophage). To do this the major head protein subunits must be able to interact with one another in *equivalent* and *quasi-equivalent* ways that involve several protein-protein interactions for each subunit monomer. For example, the different head structures for different types of phage heads shown in Figure 3 each show how a single protein monomer (represented by the smaller triangles) can interact with itself to form axes of 5-fold or 6-fold symmetry within the same structure. Thus, at each vertex in the structures shown in Figure 3, each monomer of the major head protein can have a 5-fold or 6-fold interaction with adjacent proteins.

Moody teaches that as the required size of the phage head increases (i.e. to encapsulate a larger viral genome) additional proteins are required to help deal with an increased requirement for quasi-equivalent interactions amongst the subunits in assembly of the head structure. For example, these proteins would include endoscaffolding or exoscaffolding proteins and/or other proteins that can remain as part of the mature phage head (e.g. page 404, last paragraph of column 1 to column 2, second paragraph; page 407, column 1 to page 408, column 2). Moody teaches that assembly of the phage head is a complex process that is liable to errors, resulting in malformed heads such as tubes, spirals or polyhedrons (e.g. page 408, column 2 to page 411, column 1). Moody further teaches that all of the larger dsDNA phage heads undergo some sort of maturation to form a more stable, stronger structure that is more resistant to mechanical or

chemical stress and that results in a simultaneous increase in head volume (e.g. page 413, column 2 to page 416, column 1). This process involves modification of at least one of the phage head proteins such as proteolytic cleavage (e.g. T-even phage) or chemical modification (e.g. phage P22, lambda or T7). In the maturation process the protein-protein interactions of the subunits of the phage head are necessarily altered, even resulting in the translocation of subunit domains from the inner to the outer surface of the phage head (e.g. in phage T4) (page 414, columns 1-2). Thus, phage head assembly is a complex process, involving multiple protein-protein interactions that change during the process and involving several different types of proteins.

Breadth of the claims: The breadth of the claims, encompassing any of the proteins displayed on the surface of the phage particle (e.g. head proteins: pE, pD, pW, pFII, pB*, pX1, pX2; tail proteins: pV, pJ, pG, pM and pT; page 22 lines 13-21), greatly increases the complexity of the invention with regard to how each potential matrix anchor protein is assembled into the phage, the role each potential matrix anchor protein plays in morphogenesis and assembly (i.e. is it dispensable for proper assembly and function?) and where within the coding region for the potential matrix anchor protein to insert the coding sequences for the polypeptide linker and preselected polypeptide in order to express a fusion protein that will allow its incorporation into the phage capsid in such a way as to allow morphogenesis and accessible display of the preselected protein on the mature phage particle.

Guidance of the specification/The existence of working examples: The specification provides specific guidance and working examples only for the major tail protein pV and the prior art is silent on fusion proteins that include the other tail proteins or head proteins of lambdoid phage. Reference to the other outer-surface proteins of the phage particle is only suggestive that

they are suitable for use in the invention by virtue of their location on the surface of the phage tail and capsid. There is no guidance within the specification as filed regarding which portions of the other potential matrix anchor proteins are dispensable for assembly and which may present suitable locations for insertion of heterologous sequences. There is no guidance within the specification as filed as to which particular nucleotide sequences within the gene encoding any potential matrix anchor protein, other than pV, is suitable for insertion of a heterologous coding sequence such that the expressed fusion protein from such a construct will not disrupt particle assembly and will allow functional, accessible display of the desired preselected polypeptide on the mature phage particle.

State of the art: The state of the art at the time of applicants' invention was high, requiring a high degree of skill in order to make and use the claimed invention. In fact, there is no guidance in the prior art regarding which portions of the potential matrix anchor proteins are dispensable for assembly and which may present suitable locations for insertion of heterologous sequences. There is no guidance within the prior art as to which particular nucleotide sequences within the gene encoding any potential matrix anchor protein are suitable for insertion of a heterologous coding sequence such that the expressed fusion protein from such a construct will not disrupt particle assembly and will allow functional, accessible display of the desired preselected polypeptide on the mature phage particle.

Predictability of the art: In general, the art of predicting how a particular protein will fold to form the structure which provides its functionality is not exact. This is because the relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its activity), is not well understood and is not predictable as evidenced by

Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and failures to make it predictable. Thus, as taught by Berendsen, it is likely that the first envisioned modification of a lambda phage head or tail protein to include a heterologous sequence would not be successful because one cannot predict a priori the final structure and functional characteristics of the fusion protein based upon primary sequence alone.

That the art of displaying a desired fusion polypeptide in an accessible manner on a phage particle is not predictable, as evidenced by applicants' own teachings. The specification discloses that the pV is present in 180-200 copies in the mature tail. The specification teaches (page 115, 1st paragraph) that addition of a linker polypeptide appears to interfere with tail assemble, since the plaques were smaller in su^+ hosts. Further, at page 126 of the specification it is disclosed that phage tails displaying beta-galactosidase contained only one to a few copies of the fusion polypeptide even though higher levels of incorporation could have been expected, indicating the fusion polypeptide interferes with some aspect of tail assembly or infection. Therefore, successful incorporation into a mature tail of pV protein fusions is somewhat unpredictable.

Each of the matrix proteins occupies a unique position in the mature particle, and performs a unique role during particle assembly. The successful incorporation into the tail of altered forms of one of the tail proteins (e.g. pV) does not provide evidence that any of the other

matrix proteins (head or tail proteins) can be similarly modified without impairing their unique role in phage assembly. With respect to the pV protein, it was known in the prior art that this protein comprised a "knob" that extended out from the surface of the phage that was dispensable. It is this "knob" that is replaced by the displayed peptide in the disclosed invention. Replacement of this "knob" with a heterologous peptide sequence would not have been expected *a priori* to interfere with phage assembly. However, as disclosed in the instant specification it was necessary to replace the knob with the desired peptide in only a limited number of recombinant pV subunits in the phage tail, or assembly was impaired. It is for this reason that Ladner is not deemed to be prior art for the prophetic disclosure of using pV peptide fusions to display proteins. No comparable dispensable peptide sequence is disclosed in either the specification or prior art that one could have expected could be replaced with a desired peptide, without interfering with phage assembly. As recited in the claims, the fusion polypeptide comprises, from amino to carboxy terminus, a matrix anchor polypeptide, a linker polypeptide and a preselected polypeptide. Such an arrangement would therefore require that the carboxy terminus of a given matrix anchor protein be exposed on the surface of the particle and that the addition of other polypeptides to the carboxy terminus of the matrix anchor polypeptide not interfere with either expression of the matrix anchor gene or assembly of the matrix anchor/preselected polypeptide fusion into the phage.

Applicants have submitted Mikawa et al (Exhibit 1, Paper No. 8) as evidence of enablement for other capsid or tail proteins. However, Mikawa et al is not prior art and it is not clear that the methods used to obtain phage displaying polypeptides as pD fusions are commensurate with the teachings of the instant disclosure. For example, amino terminal fusions

were made between the second and third codons, rather than at or after the initial codon (page 22, column 1). It is also noted that the primary author, Y.G. Mikawa, is not a named inventor on the instant application, which suggests that the contribution of Y.G. Mikawa is in addition to the instant disclosure. With regard to the predictability of making fusions comprising pD as the matrix anchor portion of the fusion polypeptide, it is of note that the reference states in the first paragraph of the discussion (page 27) that the ends of pD are not involved in the interaction between pD subunits or between pD and pE subunits, "...an important result for which no guarantee existed at the start of this work.". As indicated above, there is no teaching or working example in the instant specification that indicates where in the pD coding sequence (or in the coding sequence of any of the other potential matrix anchor proteins) it is appropriate to insert coding sequences for the linker polypeptide and the preselected protein such that interaction among capsid components is not interrupted, that phage assembly is not impaired and the desired fusion protein is displayed in a functional, accessible manner. Also, as with pV, one cannot extrapolate from pD fusions where to make fusions to other capsid proteins, such that phage assembly is not impaired. Mikawa et al specifically states that the authors chose pD because it was dispensable provided the genome was less than 82% of wild type in length, a feature not true for the other capsid proteins.

The amount of experimentation necessary: Given the complex nature of the invention in which a fusion polypeptide comprising an anchor motif from the bacteriophage matrix is expressed during phage morphogenesis such that the fusion polypeptide is incorporated into the phage structure and displayed in an accessible and/or functional manner, the breadth of the claims which encompass any of the potential matrix anchor polypeptides displayed on the

surface of the phage particle, the lack of guidance from the specification or the prior art as to which portions of any of the other potential matrix anchor proteins are dispensable for phage assembly or which would be appropriate for insertion of the coding sequences for the polypeptide linker and preselected polypeptide (even for pD) and the unpredictability of whether a particular fusion will be incorporated into the phage particle in a fashion that does not disrupt subunit-subunit interaction and will allow accessible and/or functional display of the desired, preselected polypeptide on the mature particle, it would require undue, unpredictable experimentation to make even one embodiment of the claimed invention not involving pV as the matrix anchor protein. One would first have to envision an appropriate matrix anchor protein construct in which the coding sequence for the matrix anchor protein is operatively linked at a particular sequence with the coding sequences for a linker polypeptide and desired, preselected polypeptide, make the construct and express the hybrid gene during morphogenesis such that the fusion protein might be incorporated into the phage particle and then determine whether functional phage particles are formed which display the desired, preselected polypeptide sequence in an accessible and/or functional manner. If unsuccessful, which is likely given the lack of guidance from the specification or the prior art as to which portions of the other potential matrix anchor proteins are dispensable for particle assembly and the unpredictability of the art as evidenced by applicants' own teaching regarding pV, it would then be necessary for one of skill in the art to envision a modification of the first matrix anchor/fusion protein construct, or an entirely different construct, which might be suitable for display of a desired protein on the surface of the phage particle, make the construct and express the hybrid gene during morphogenesis such that the second fusion protein might be incorporated into the phage particle

and then determine whether functional phage particles are formed which display the desired, preselected polypeptide sequence in an accessible and/or functional manner. If again unsuccessful, which is likely given the lack of guidance from the specification or the prior art as to which portions of the other potential matrix anchor proteins are dispensable for particle assembly and the unpredictable nature of the art as evidenced by applicants' own teachings regarding pV, it would be necessary for one of skill in the art to repeat the entire process until such time, if any, that a construct was identified which allows the expression of a fusion protein comprising one of the potential matrix anchor proteins with a desired, preselected polypeptide such that the fusion protein is successfully incorporated into the mature phage particle and the preselected polypeptide displayed in an accessible and/or functional manner. Such experimentation is undue, unpredictable experimentation and would be required in order to make and use any embodiment of the instant invention not comprising pV as the matrix anchor portion of the fusion protein, even the pD fusions of Mikawa et al, in light of the instant specification. Thus, applicants' claimed invention of a recombinant lambdoid bacteriophage vector or bacteriophage encoding protein fusions derived from any matrix anchor protein located on the surface of the phage particle operatively linked to a polypeptide linker and preselected polypeptide, is not considered to be fully enabled by the specification. Only in the case where the matrix anchor protein is derived from the pV polypeptide, as described in the specification, would there be a reasonable expectation of success in constructing a vector or bacteriophage which encodes a fusion polypeptide comprising the desired, preselected polypeptide expressed and displayed in an accessible and/or functional manner.

Response to Arguments

Applicant's arguments filed on 9/15/03 have been fully considered but they are not persuasive. The response essentially argues: **1)** the reliance by the examiner on the teachings of Moody is immaterial and irrelevant, **2)** the examiner relies upon Moody to establish the unpredictability of using a particular anchor matrix protein to form a phage particle displaying the protein on its surface, **3)** the examiner's reliance on applicants' own data is faulty and irrelevant (e.g. the number of copies of the fusion protein displayed on the surface is not a claim limitation and the specification teaches in detail that other phage proteins are present in greater numbers than pV), **4)** the examiner has failed to recognize that the teachings of Mikawa et al use virtually the identical procedure for expression of a phage using pD as that taught in the instant specification (e.g. on page 25-28 Mikawa et al teach λfoo for expressing pD fusions, the same vector taught in the instant application), and **5)** given that the pD protein fusions taught by Mikawa et al are head proteins, this is explicit proof the instant specification is enabling for both head and tail proteins.

The teachings of Moody concerning the great complexity of phage morphogenesis are entirely relevant in terms of establishing the complexity and unpredictability of making and using the claimed invention, for the reasons outlined above. Moody makes clear why it would require detailed teachings concerning the role a particular phage protein plays in particle assembly in order to reliably make and use a bacteriophage comprising a fusion protein made from one of the head proteins. No such explicit guidance is given anywhere in the specification for pD or any other head protein.

With regard to applicants' own data concerning pV, it is true that the copy number of the fusion protein is not a recited claim limitation. The examiner cited applicants' own data to demonstrate it was unpredictable beforehand even for applicants' sole exemplified embodiment of the invention whether a mature particle would be formed. Applicants' data showed that it was in fact necessary to express at least some "wildtype" copies of pV in order to avoid impairing assembly. Applicants' implied assertion that the examiner was somehow imposing a limitation of "copy number" on the rejected claims is inaccurate. In fact, one could argue that a greater copy number present in the phage head for a wildtype phage protein would probably mean a greater probability of any alteration in that protein resulting in impaired assembly of the phage particle.

To assert that because Mikawa et al use the lambda vector λfoo to express their pD fusions, applicants' teachings use a "virtually identical procedure" is stretching a point. Yes, the same expression vector by Mikawa et al, yet the specifics concerning the appropriate points for insertion of the heterologous sequences within gene D were not taught in the instant specification. With regard to the predictability of the art at the time of filing, Mikawa et al make clear that it would have been unpredictable to make and express pD fusions such that the fusion protein is functionally displayed on the surface of a phage particle because the nature of pD interactions during phage assembly were not known. The reference states in the first paragraph of the discussion (page 27) that the ends of pD are not involved in the interaction between pD subunits or between pD and pE subunits, "...an important result for which no guarantee existed at the start of this work.". Again, given the very limited teachings from the instant specification, and the complexity/unpredictability of the art as evidenced by both Moody and Mikawa et al, it

would have required unpredictable trial-and-error experimentation in order to construct and use pD fusions at the time of the invention.

The assertion that the data presented by Mikawa et al for pD fusions can be interpreted as evidence that the instant specification is enabling for the use of any head or tail protein is inaccurate for reasons of record. To summarize, phage assembly is an extraordinarily complex process, involving multiple protein:protein interactions that must occur in the correct temporal and spatial manner in order for a mature phage particle to form. Simply asserting that the ability of one phage protein to function as a matrix anchor for the display of a functional fusion protein does not take into account the evidence of record concerning the complexity of phage assembly and does not assess what was known in the art at the time of the invention concerning specific protein:protein interactions for assembly of lambda phage particles. Thus, even if one were to accept the teachings of Mikawa et al as evidence that the instant specification was enabling for the generation and use of pD fusions, which is in no way conceded here, there is no basis for extending the teachings of Mikawa et al to the other phage proteins.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

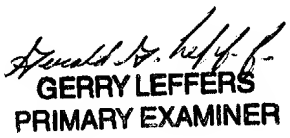
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



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Primary Examiner
Art Unit 1636

Ggl